

**REMARKS**

**A. The Status of the Claims and the Amendments**

By the present amendment, claims have been amended to more particularly define the Applicants' invention and to claim it with greater specificity. New claims 82-114 have been added. The amendments to claims and the new claims are supported by the specification and the original claims. No new matter have been added. Claims 12 and 13 were previously withdrawn from consideration as directed to non-elected species, and claims 1, 2, 5-11, 14-16, 18-21, and 36-60 were previously canceled.

Claims 66-81 were previously allowed (see, Office Action mailed 12/26/2006). The Applicants acknowledge the fact that the Examiner has now withdrawn the previously indicated allowability "in view of further consideration of the prior art of record." The Applicants respectfully submit that such an action is improper. Indeed, the "prior art of record" mentioned by the Examiner is the Unger reference (WO 96/40285) ("Unger").

This reference has been before the Examiner throughout the entire process of examination, and raising this rejection over Unger now, for the first time, amounts to piecemeal examination, which is improper. It is well established that an Office Action must be complete as to all matters, and, if a claim is rejected, an examiner is required to provide every valid ground for rejection. See, 37 CFR § 1.104 and also MPEP § 707.07(g). The Applicants respectfully submit that they don't understand why this rejection were not made previously, when the Examiner had every opportunity to make it. The Applicants also respectfully request that the Examiner explain what the "further consideration" is that led to the withdrawal of the previously indicated allowability of claims 66-81.

After the present amendment has been entered, claims 3, 4, 17, 22-35, 61, and 63-114 will be under consideration. It is submitted that the amendments place all the claims that have not been previously allowed in condition for allowance. Entry of the amendments is respectfully requested.

**B. Rejection Under 35 U.S.C. § 103(a)**

Claims 3, 4, 6-10, 17, 22-35, 61 and 63-81 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Unger (WO 96/40285). This rejection is respectfully traversed on the following grounds.

The standard that has to be satisfied in order to make a valid rejection based on a prima facie case of obviousness was described in a response to a previous Office Action. This standard has been modified recently by the recent Supreme Court decision in the KSR International v. Teleflex Inc., 127 S.Ct. 1727, 82 USPQ 2d. 1385 (2007), and there is no longer a strict requirement to satisfy the old “teaching-suggestion-motivation” standard to show obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the art and common sense may be considered when determining the feasibility of modifying and/or combining references. The Applicants respectfully submit that the Examiner has not established a prima facie case of obviousness either under the old standard or according to the modified standard.

More specifically, claim 17, as amended, has been modified and the structure recited in the claim has been slightly simplified. Claim 17 now shows a general structure, on the right side of which there is one of the following two moieties

(a) if  $R^7$  is a direct bond,  $-P-C(O)-T$ ; or

(b) if  $R^7$  is  $(CH_2)-(CH_2)$ ,  $-P-(CH_2)-(CH_2)-C(O)-T$ .

Therefore, the targeting ligand T must be connected to PEG either via a carbonyl  $-C(O)-$ , as in moiety (a), or via the di-methylene-carbonyl bridge, as in moiety (b). Claim 17 is clearly presented in such a way that no other moiety can appear on the right side to connect the targeting ligand T to PEG. The same applies to claim 66, where only the moiety (b) can be present to connect PEG and the targeting ligand T.

Unger fails to describe or suggest a compound that satisfies these limitations. Indeed, in Unger  $X_3$  is the element that is the equivalent, location-wise, to the bridging moiety presented in claims 17 and 66, because  $X_3$  is situated between the hydrophilic polymer Z (which the Examiner considers as corresponding to PEG in the current claims) and the targeting ligand Q (see the formula in Unger, on page 61 below line 2).

As can be seen,  $X_3$  in Unger cannot be either moiety (a) or moiety (b). Unger describes the possible moieties that can represent  $X_3$ . All of them (other than  $X_3$  being a direct bond) require (page 61, lines 6-8) that there must be  $X_4$  next to the carbonyl group  $-C(=X_5)-$  (i.e., when  $X_5$  is O). The possibilities for  $X_4$  are limited in Unger to the ether bond  $(-O-)$ , an amino group  $(-NR_4-)$ , or a thioether group  $(-S-)$  (see, Unger, page 61, line 9).

There is nothing in Unger, disclosing or suggesting the possibility of a direct bond, with or without the di-methylene bridge, between the carbonyl group and the polymer Z. Yet, this is clearly required by claims 17 and 66, as amended. Nor is there anything at all in Unger that would provide one skilled in the art with motivation to modify Unger as suggested by the Examiner, or a possibility of any reasonable expectation of success stemming from such modification. Neither the general state of the

art nor common sense would lead to the conclusion that such modification of Unger is desirable or feasible.

The Examiner then stated (page 5, last paragraph of the Office Action) that if in Unger  $X_3 = -R_5-(C=X_5)-X_4$ , and  $R_5$  is an alkyl,  $X_5$  is O, and  $X_4$  is N, then it would anticipate a compound of claim 17 having the structure  $-(CH_2)-(CH_2)-C(O)-T$  (i.e., the moiety (b) shown above. In the Examiner's view there is inherently an amide bond formed by the carbonyl  $-C(O)-$  and the amino group inherently donated by the peptide T.

The Applicants respectfully disagree. The compound recited in claims 17 and 66 requires the amide bond formed between  $-C(O)-$  and the amino group of the amino terminus of cysteine. Unger does not have nor suggests such an amide bond. Indeed, Unger clearly teaches only  $X_4 = -NR_4-$ , not  $X_4 = N$ . Thus, if  $R_4$  is H, the right hand side of  $X_3$  must be amino group. In such a case, the only way to form an amide bond here, will be using this amino group and a carboxyl of the peptide Q, which will obviously require that the carboxy terminus of Q be on the left-hand side.

In other words, each of claims 17 and 66, under the Examiner's analysis, will have a  $-C(O)-NH-$  moiety connecting the targeting ligand T to the right of  $NH-$  to the rest of the molecule to the left of  $-C(O)$ . At the same time, Unger would show a reversed picture, i.e.,  $-NH-C(O)-$  moiety connecting the targeting ligand Q to the right of  $C(O)-$  to the rest of the molecule to the left of  $-NH$ . Accordingly, claims 17 and 66 on the one hand, and Unger on the other hand describe different compounds, and there is no indication or suggestion that their properties or potential uses may be similar.

In view of the foregoing, each of claims 17 and 66, as amended, is considered patentably distinguishable over Unger. Each of claims 3, 4, 6-10, 22-35, 61, 63-65, and 67-81 directly or indirectly depends on either claim 17 or claim 66, and is patentably allowable for at least the same reason. Reconsideration and withdrawal of the rejection of claims under 35 U.S.C. §103(a) are, therefore, respectfully requested.

**C. New Claims**

New claims 82-114 have been presented by the current amendment. Claims 82-98 all depend on claim 17 and include the moiety  $X^1$  is  $C(=X^3)$ . Claim 99 is independent, but is similar to claim 66, except the scope of claim 99 is also limited to the embodiments where  $X^1$  is  $C(=X^3)$ . Claims 100-114 all depend on claim 99 and are, therefore, also limited to the embodiments where  $X^1$  is  $C(=X^3)$ .

It is submitted that the Unger reference does not describe nor suggest any compounds having either M or  $X_2$  being carbonyl. See definitions of M and  $X_2$  in Unger (page 61, lines 6-8 and 11-12). Thus, the new claims 82-114 are patentably distinguishable over Unger. Accordingly, allowance of claims 82-114 is respectfully requested.

**CONCLUSION**

In view of the above amendments and remarks, reconsideration and favorable action on all claims are respectfully requested. In the event any matters remain to be resolved, the Examiner is requested to contact the undersigned at the telephone number given below so that a prompt disposition of this application can be achieved.

No fee is deemed to be due in connection with this response. However, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896, referencing the above-referenced Attorney docket number.

Respectfully submitted,

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